REMARKS

This Amendment and Remarks are in response to the Office Action dated October 3, 2002 ("Office Action"). This Reply is filed along with a petition for a three (3) month retroactive extension of time and authorization to charge a charge account the appropriate statutory fee for extension.

Claims 28-70 were pending at the time of the Office Action and all claims were rejected. Applicants have amended claims 28, 29, 31, 50, 66-68 and 70, and have cancelled claims 45-47. A Marked-Up Version To Show Claim Amendments using standard underlining and bracketing format to highlight the changes made is attached herein. No new matter is presented.

In paragraph 1 of the Office Action, the Examiner has determined that the application contains claims directed to the following patentably distinct species being:

a) coated drug particles where the coating is continuous, and

b) coated particles where the coating is discontinuous.

Based on the above species determination, Applicants are required to elect a single disclosed species from a) and b) for prosecution on the merits to which claims will be restricted if no generic claim is finally held to be allowable. In response, without traverse, Applicants hereby select species (b) comprising a continuous coating, and have amended independent claims 28, 29, 66 and 68 to reflect this selection. Claim 46 and its dependent claim 47 relating to a discontinuous coating are hereby cancelled, without prejudice.

In paragraph 6 and 11 of the Office Action, claims 66-67 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims were also rejected under 35 U.S.C. §101 because "the claimed recitation of a use, without setting forth any

steps involved in the process, results in an improper definition of a process; i.e., results in a claim which is not a proper process claim under §101". In response, amended claim 66 now directly recites method steps, and amended claim 67 is now made dependent on claim 66. Accordingly, the above 35 U.S.C. § 112, second paragraph, and 35 U.S.C. §101 rejections of claim 66 and 67 are now overcome.

In paragraph 9 of the office Action, claims 46 and 47 were rejected for "failing to further limit the claim to which it refers". In response, as noted above, both of these claims have been cancelled. Accordingly, the above rejections of claims 46 and 47 are now overcome.

The claim rejections are summarized in a table shown below:

Claims		Reference(s)
28-45, 48, 50-54, 59-61		U.S. Patent No. 5,223,244 to Moro, et al.
48		Moro in view of U.S. Patent No. 4,678,772 to Segal, et al.
28-45, 48-61, 66-67		U.S. Patent No. 5,972,388 to Sakon, et al.
28-45, 48, 59-61, 66-67		U.S. Patent No. 5,855,913 to Hanes, et al.
49, 56-58		Hanes, et al., in combination with U.S. Patent No. 6,129,905 to Cutie, and further in combination with Goodman and Gilman
62-65		Hanes, et al., in view of U.S. Patent No. 6,277,364 to Bucks, et al., or U.S. Patent No. 5,972,388 to Sakon, et al, in view of Bucks, et al, or over Moro, et al., in view of Bucks, et al.

In addition, method claims 68-70 were rejected based on claims 1-36 of the Talton patent (US 6,406,745; hereafter Talton '745) based on a determination of non-statutory obviousness-type double patenting. No other art was cited against the method claims.

In addition, again regarding double patenting, the Office Action determined that "should claim 28 be found allowable, claim 50 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof". In response, claim 50 has been amended to now recite "a pharmaceutically acceptable solution". Support for this amendment can be found on page 12,

lines 13-33 of Applicants' specification. Accordingly, claim 50 as amended cannot be considered to be a substantial duplicate of claim 28.

Before reviewing the cited art, Applicants will first review the claimed invention as recited in amended claim 28. Amended claim 28 recites a medicament comprising a plurality of coated drug particles, each coated particle having an average particle size of less than 500 μm in diameter, the surface of the particles comprising at least a first layer of coating particles. The coating layer is a continuous and non-porous layer. The coating particles are biodegradable or biocompatible. The biodegradable or biocompatible coating layer provides controlled drug delivery and increases the bioavailability of drug particles. The average thickness of the coating layer is from 1 to 500 nm. Amended claim 68 recites a closely related claim relating to a method of preparing a coated drug particle.

The laser ablation process can be used to produce very thin (1 to 500 nm) continuous and non-porous coating layers on core drug particles. Such thinly coated medicaments are not possible using other known methods for coating core drug particles (see page 1, lines 23-30). Core drug particles having very thin continuous and non-porous coatings are evidenced by sustained release profiles which are provided throughout Applicants' specification. Continuously coated core particles are the antithesis of non-continuously coated core particles, such as those coated with porous coatings. Porous or other non-continuous coatings clearly cannot provide sustained release profiles.

For example, Example 2 (beginning on page 34, line 28) demonstrates an improved sustained release rate profile compared to the uncoated drug particles. A 90% release occurred at approximately 12 hours (for coating at 2 hertz) and beyond 24 hours (coating at 5 hertz), compared to uncoated drug particles that reached 90 % release at approximately 2 hours (see

Figs. 6 and 7). Similarly, in Example 3 (page 36, lines 11-14), in vitro dissolution of coated rifampicin reached 90% release after 6 hours compared to 90% release after 15 minutes for the uncoated rifampicin (Fig. 8).

The three main referenced relied on by the Examiner, Moro, Sakon and Hanes, are all examples of spray drying processes, with Moro including a dry mixing process to form particles which are then spray dried onto a skin surface. Spray drying is a process that is quite distinct as compared to laser ablation, and produces particle mixtures which are also quite distinct as compared to the claimed coated drug particles. Spray drying is a process by which a plurality of species are generally first dissolved in a solvent containing solution. In some processes, one or more species may be insoluble in the solvent containing solution.

The solution is sprayed and then drying takes place. In Moro, the spray is applied to a skin surface where it dries. In Sakon and Hanes, spray-drying occurs by spraying into an open chamber where the particles dry rapidly from a heated air-flow, generally from below, and the particles are suspended to aid drying. Either way, the solvent and other volatile species rapidly evaporate to leave a random mixture of the remaining non-volatile species intermixed. No distinguishable coating layer is formed on any species since the arrangement of particles following drying is random. Accordingly, as known by those having ordinary skill in the art, spray drying does not form coated particles, and clearly cannot provide Applicants' claimed medicament comprising a core drug particle coated with a continuous and non-porous coating layer as evidenced by the dissolution profiles provided in Applicants' specification.

speculation

see Remington or spray drying

Dry mixing is also a process that is quite distinct as compared to laser ablation, and produces a mixture of particles which are also quite distinct as compared to the claimed coated drug particles. In dry mixing, as the name suggests, two (or more) distinct powders are poured

into a bowl and stirred or placed in a bead mill to randomize the mixture so that sampling any discrete volume within the overall sample has the same percentage of the respective components. As known by those having ordinary skill in the art, the resulting particle mixture in dry mixing is always porous and agglomeration of like particles is also generally present.

Turning now to statutory claim rejections based on cited art, Moro was determined to anticipate the claimed invention. According to the Examiner:

> '244 discloses aerosol compositions comprising a powder coated with a sheath powder. The average particle size of the core powder is 0.1 μm to 100 μm and the sheath powder is 1/5 the size of the core powder (Col. 2, Line 12-44; Col. 3, Line 24-27; examples; claims, especially 6-7). '244 also discloses that the active agent is glycyrrhizinate and that the weight percent is within the instant ranges. '772 is relied upon for disclosing that glycyrrhizin is an anti-inflammatory agent. '244 also discloses inclusion of propellant in the aerosol formulations.

Moro discloses an aerosol composition containing a composite powder and one or more of propane, isobutane, n-butane and a liquefied petroleum gas (i.e., LPG) which is a mixture thereof, a chlorinated hydrocarbon and dimethyl ether. The composite powder is formed using a dry mixing process (see col. 3, lines 38-62), such as a mixer with a ball shaped mixing medium.

As noted above, the composite powder is inherently porous. Although Moro discloses the "core powder" can be "substantially completely covered by the coating powder" (col. 4; line 35-36) and in another specification portion being completely covered based solely on a SEM image in Example 2, Moro never describes any coating as being non-porous, because dry mixing cannot form non-porous coatings on core particles due to the random nature of the resulting particle distribution. In addition, none of the sheath or core powders disclosed by Moro are drugs.

claims don't specify such

The porous composite powder is then used as one of the components in the aerosol. Although the aerosol solutions disclosed generally do not include any drugs, in one embodiment,

identified as example 10 and entitled a "POWDER SPRAY" an aerosol spray including potassium glycyrrhizinate is disclosed. The aerosol including the composite powder is then applied to a surface, such as the skin of an individual. Thus, Moro applies the aerosol using a spray-on process.

Moro does not disclose or suggest Applicants' claimed continuous and non-porous coated core drug particles as the sheath particles disclosed by Moro do not provide a non-porous coating on the core particles whether after dry mixing or following drying after spray drying. Moreover, no drug particles are ever coated by Moro. Although in Example 10 Moro discloses glycyrrhizinate which can be used as an anti-inflammatory, the composite powder is granular tetrafluoroethylene (1μm) with a 0.1 μm kaolin coating, neither of which are drugs. The composite powder is insoluble in the disclosed mixture. The only drug (potassium glycyrrhizinate) is freely soluble in the disclosed solvents of ethyl alcohol and water. (See attachment "A" provided from the Merck Index, Tenth Edition page 647 regarding the solubility of glycyrrhizic acid).Upon spraying and drying, a random mixture of potassium glycyrrhizinate, tetrafluoroethylene and kaolin results. Thus, Moro does not disclose or suggest Applicants claimed continuous and non-porously coated drug particles.

Moreover, Moro's aerosols includes toxic species, such as hydrocarbons and dimethyl ether which are clearly not compatible with Applicants' claimed coated drug particle. Residues of these toxins which remain following the drying process would prevent use of the resulting mixture as a medicament. In view of the above noted distinctions, Applicants submit that amended claim 28 and all claims dependent thereon are patentable over Moro.

Claim 28 was rejected as being obvious based on Sakon. According to the Examiner:

'388 (Sakon) teaches an ultrafine particle powder for inhalation where the particle powder is produced by spray-drying a mixture of active agent and a lower alkyl ethyl cellulose where the

active [agent] and the cellulose are either dissolved or suspended in a solution and then spray-dried into particles that are as small as 500 nm. Particles smaller than this size do not appear to be critical since size criticality appears to depend on administration to lower airways which is achieved with '388. Such is also the case for the thickness of the coating layer. '388 also teaches that the active triamcinolone acetonide or a bronchodilator and that mixtures of actives are contemplated.

Sakon discloses an ultrafine particle powder mixture for inhalation produced by spray-drying to be delivered mainly to a lower airway, containing specific cellulose lower alkyl ethers and a medicament, at least 80% of the powder having a particle size in the range of 0.5 to 10 μm. Thus, Sakon is similar to Moro as both disclose use of spray-on process variants.

Sakon's components are all dissolved in solution. After being sprayed and upon drying of the applied spray, Sakon forms random mixtures including drugs, not Applicants' claimed continuous and non-porously coated medicaments. As noted in the excerpt below, the medicaments are in the form of fine mixtures with cellulose particles. According to col. 10, lines 13 to line 29:

> The ultrafine particle powder for inhalation of the invention is required to have pharmaceutically acceptable macroscopic mixing uniformity. That is, any portion of the powder is always required to have a uniform medicament concentration. Moreover, the ultrafine particle powder for inhalation of the invention is required to be in a microscopically uniform mixed state which is pharmaceutically acceptable, and as a result the percentage composition of a fraction thereof delivered to and deposited in a respiratory apparatus of a human should agree with the entire percentage composition thereof. Although the ultrafine particle powder for inhalation of the present invention *should be microscopically in a uniform mixed state, the medicament may be completely mixed with a cellulose lower alkyl ether, in an amorphous state, or it may be dispersed therein, in a microcrystalline state, or it may be in an intermediate state between the above-mentioned two states.* (italics for emphasis)

Always producing a particle mixture by their method as noted above, it is not surprising Sakon does not mention any sustained release profiles. Since Sakon only discloses particle mixtures and does not disclose or suggest Applicants coated medicaments, the coating being

continuous and non-porous, Applicants submit that amended claim 28 and all claims dependent thereon are patentable over Sakon.

Claim 28 was determined to be obvious based on Hanes. According to the Examiner:

> '913 (Hanes) teaches aerodynamically light particles for inhalation where the particles are produced by emulsifying active agent in polymer such as PLA or PLGA in a volatile solvent. After mixing, the mixture is sprayed-dried and the volatile solvent is evaporated to leave drug particle enclosed by polymer. The particles of '913 are as small as 2 μm. Particles smaller than this size do not appear to be critical since size criticality appears to depend on administration to lower airways which is achieved by '388. Such is also the case for thickness of the coating layer.

Hanes discloses aerodynamically light particles incorporating a surfactant on the surface thereof for drug delivery to the pulmonary system, and methods for their synthesis and administration. In a preferred embodiment, the aerodynamically light particles are made of a biodegradable material and have a tap density less than 0.4 g/cm^3 and a mass mean diameter between 5 μm and 30 μm. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of poly(lactic acid) or poly(glycolic acid) or copolymers thereof. Alternatively, the particles may be formed solely of the drug or diagnostic agent and a surfactant. Surfactants can be incorporated on the particle surface for example by coating the particle after particle formation, or by incorporating the surfactant in the material forming the particle prior to formation of the particle. Exemplary surfactants include phosphoglycerides such as L-alpha-phosphatidylcholine dipalmitoyl. The aerodynamically light particles incorporating a therapeutic or diagnostic agent and a surfactant may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of wide a variety of therapeutic agents.

Similar to Moro and Sakon, Hanes also uses a spray-drying process. Example 2 describes Synthesis of Spray-Dried Particles. According to col. 11, line 55 to col. 12, line 13:

Aerodynamically Light Particles Containing Polymer and Drug Soluble in Common Solvent

Aerodynamically light 50:50 PLGA particles were prepared by spray drying with testosterone encapsulated within the particles according to the following procedures. 2.0 g poly (D,L-lactic-co-glycolic acid) with a molar ratio of 50:50 (PLGA 50:50, Resomer RG503, B.I. Chemicals, Montvale, N.J.) and 0.50 g testosterone (Sigma Chemical Co., St. Louis, Mo.) are completely dissolved in 100 mL dichloromethane at room temperature. The mixture is subsequently spray-dried through a 0.5 mm nozzle at a flow rate of 5 mL/min using a Buchi laboratory spray-drier (model 190, Buchi, Germany). The flow rate of compressed air is 700 nl. The inlet temperature is set to 30 C. and the outlet temperature to 25 C. The aspirator is set to achieve a vacuum of -20 to -25 bar. The yield is 51% and the mean particle size is approximately 5 μm. Larger particle size can be achieved by lowering the inlet compressed air flow rate, as well as by changing other variables. The particles are aerodynamically light, as determined by a tap density less than or equal to 0.4 g/cm^3. Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors.

According to col. 13, line 58 to col. 14, line 5:

Microsphere Preparation: Spray Drying

The model hydrophilic drug, dextran labeled with fluorescein isothiocynate (FITC-Dextran), was encapsulated into PLA or PLGA by a novel emulsion/spray method. For example, 2.0 ml of an aqueous 10% w/v FITC-Dextran (MW=70,000, Sigma Chemical Co.) solution was emulsified into 100 ml of a 2% w/v solution of PLA in dichloromethane by probe sonication. The emulsion was subsequently spray-dried using a Buchi Mini Spray Drier (Model 190, Buchi Instruments, Germany) at a flow rate of 5 ml/min with an inlet air flow rate of 700 nl/h, inlet temperature of 30 C., outlet temperature of 21 C., and vacuum of -20 mbar. When DPPC was incorporated it was dissolved in the polymer solution at a concentration of 2 mg/ml prior to emulsification and spray drying.

Thus, Hanes teaches spray drying a mixture including a polymer and a drug or diagnostic agent. The polymer and drug or diagnostic agent are dissolved in solution. Upon drying, a random mixture results including the polymer and the drug or diagnostic agent, not Applicants' claimed medicament having a continuous and non-porous coating. Thus, Applicants submit that claim 28 and all claims dependent thereon are patentable over Hayes.

Amended claim 29 (product by process) now recites the same patentable continuous and non-porous coated medicament features which are now recited in amended claim 28, as does amended claim 50 (pharmaceutical formulation), amended claim 62 (kit), and amended claim 66.

Regarding method claims 68-70, claims 1-36 of the Talton patent (US 6,406,745) were cited under non-statutory obviousness-type double patenting. No other art was cited against the method claims. Although Dr. Talton is an inventor on both the cited art and the present invention, Applicants respectfully disagree that the claimed invention is obvious based on Talton '745 as explained below.

Applicants first note that claim 68 has been amended to now recite a vacuum between 1 mTorr and 1 Torr. Support for this limitation can be found on page 22, lines 8-9. The claimed vacuum level of between 1 mTorr and 1 Torr further distinguishes the claimed method from Talton '745.

Talton discloses methods of coating core materials by providing target materials and core materials; ablating the target materials to form ablated particulate target materials; and coating the core materials with the ablated particulate target materials. The method is performed at *a pressure of 10 Torr or higher*. Methods of coating particles with nanometer to multiple nanometer thick coatings in atmospheric pressure, and using pneumatic fluidization, are also provided. (italics for emphasis only)

Although Talton '745 discloses use of a vacuum of as low as 10 Torr, Talton teaches preferentially ablating at atmospheric pressure (760 Torr). According to col. 7, line 1 to line 12:

> The invention is operated such that the coating chamber has a pressure of around atmospheric pressure, which may be a pressure as low as about 10 Torr to as high as about 2500, or any pressure in between. Preferably, the pressure in the coating chamber is greater than about 20, or 30, or 40, or 50 Torr, more preferably greater than about 100 or 500 Torr, and most preferably greater than about 700 Torr. Preferably, the pressure in the coating chamber is less than about 1000, more

> preferably less than about 900, and most preferably less than about 820. *In a most preferred embodiment, the pressure in the coating chamber is about 760 Torr, or atmospheric pressure.* (italics for emphasis only)

Moreover, Talton' 745 teaches significant advantages of operation at a comparatively higher pressure as compared to the claimed method. According to col. 6, line 44 to line 48:

> Operating the coating process at approximate atmospheric pressure allows for a continuous production process. Rather than needing to apply a vacuum on each batch for coating, the process of the present invention, operated at near atmospheric pressure, allows for continuous processing.

Thus, Talton '745 does not disclose or suggest an ablation process under a vacuum of less than 10 Torr, and in fact teaches away from use Applicants' claimed mTorr range vacuum level. Use of a lower pressure (less than 10% of the lowest pressure disclosed in Talton '745) provides significantly smaller particles and a coating layer having higher purity (less ambient inclusion) as compared to the vacuum level disclosed in Talton '745. Accordingly, Applicant submit that the double patenting rejection of claims 68-70 based on Talton '745 should be removed.

Applicants have made every effort to present claims which distinguish over the cited art, and it is believed that all pending claims are in condition for allowance. However, Applicants request the Examiner to call the undersigned after review of this Reply if the Examiner determines that any clarification is necessary to permit issuance of a Notice of Allowance.

Respectfully submitted,

Date: 4/02/03

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Docket No. 5853-186US

28. (Amended) A medicament comprising a plurality of coated drug particles, each of said coated drug particles having an average particle size of less than 500 μm in diameter, the surface of said particles comprising at least a first coating layer of biodegradable and bio-compatible material, said coating layer being a continuous and non-porous layer, wherein an average thickness of said coating layer is between 1 and 500 nm.

29. (Amended) A medicament comprising a plurality of coated drug particles, each of said coated drug particles having an average particle size of less than 500 μm in diameter, the surface of said particles comprising at least a first coating layer of biodegradable and bio-compatible material, said coating layer being a continuous and non-porous layer, wherein an average thickness of said coating layer is between 1 and 500 nm, the coated drug particles being obtainable through a process comprising depositing said polymeric coating particles onto the surface of host drug particles by a process comprising pulsed laser ablation.

31. (Amended) The medicament according to claim 28, wherein said [coated drug particles have an average particle size of less than 100 μm in diameter] medicament consists essentially of said plurality of said coated drug particles.

50. (Amended) A pharmaceutical formulation comprising the medicament of claim 28 and a pharmaceutically acceptable solution.

66. (Amended) A method for treating patients, comprising the steps of:

providing a medicament comprising a plurality of coated drug particles, each of said coated drug particles having an average particle size of less than 500 μm in diameter, the surface of said particles comprising at least a first coating layer of biodegradable and bio-compatible material, said coating layer being a continuous and non-porous layer, wherein an average thickness of said coating layer is between 1 and 500 nm, and

[The use of coated drug particles as defined in claim 28 for the manufacture of a medicament for] treating a respiratory disorder or pulmonary infection in a human patient using said medicament.

67. (Amended) The method of claim 66, wherein said medicament is a pharmaceutically-acceptable formulation [use of a formulation according claim 50 for the manufacture of a medicament for treating a respiratory disorder or a pulmonary infection in a human patient].

68. (Amended) A method of preparing [the] a medicament [of claim 28], the method comprising the steps of:

providing a plurality of core drug particles, each of said core drug particles having an average particle size of less than 500 μm in diameter, and

"Core" = New Matter

depositing onto the surface of [a] said plurality of core [host] drug particles at least a first coating layer that comprises a plurality of polymeric coating particles, said coating layer being biodegradable, bio-compatible, wherein an average thickness of said coating layer is between 1

and 500 nm, said depositing step by a process comprising pulsed laser ablation under vacuum, wherein said vacuum is between 1 mTorr and 1 Torr.

70. (Amended) The method according to claim [69] 68, wherein said coating layer is continuous and non-porous [pulsed laser ablation process comprises providing a laser which emits radiation having a wavelength of about 248 nm].

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RAHWAY, N.J., U.S.A.

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Library of Congress Catalog
Card Number 83-61075
ISBN Number 911910-27-1

Printed in the U.S.A.

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cylglycine: Sheehan, Frank, *Ibid.* 71, 1856 (1949). From the dicyclohexylamine salt of trifluoroacetylglycylglycine: Weygand, Reiher, *Ber.* 88, 26 (1955).

Crystals from dil alc. Crystal shape described as small tetrahedral leaves with a lustrous ball in center. Dec 262-264°. pK_1' 3.12; pK_2' 8.17. Heat of combustion: 472.4 kcal/mole. Soluble in hot water; slightly sol in ethanol. Practically insol in ether.

Hydrochloride, $C_4H_8N_2O_3.HCl.H_2O$, crystals from water + ethanol.

Ethyl ester hydrochloride, crystals from abs ethanol, dec 182°.

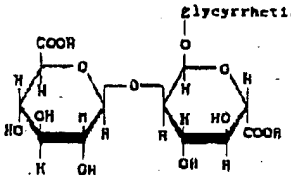
USE: In the synthesis of more complicated peptides.

4368. Glycyrrhiza. ...corice; liquorice; sweet root. Dried rhizome and ro... of *Glycyrrhiza glabra* L., var. *typica* Regel & Herder (Spa...ish licorice), or of *G. glabra* L., var. *glandulifera* (Waldst. & Kit.) Regel & Herder (Russian licorice), or of other varieties of *G. glabra* yielding a yellow and sweet wood, *Leguminosae. Habit.* Southern Europe to Central Asia. *Constit.* 6-14% glycyrrhizin (the glucoside of glycyrrhetic acid), asparagine, sugars, resin.

USE: Chiefly in the form of syrup of glycyrrhiza. *Incompat.* Acids, metallic salts.

THERAP CAT: Extract and syrup as pharmaceutic aids (flavor and flavored vehicles).

4369. Glycyrrhizic Acid. *20β-Carboxy-11-oxo-30-norolean-12-en-3β-yl-2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid;* glycyrrhizin; glycyrrhizinic acid; glycyrrhetinic acid glycoside. $C_{42}H_{62}O_{16}$; mol wt 822.92. C 61.30%, H 7.59%, O 31.11%. Extraction from *Glycyrrhiza glabra* L., *Leguminosae:* Karrer, Chao, *Helv. Chim. Acta* 4, 100 (1921); Ruzicka, Lousenberger, *Ibid.* 19, 1402 (1936). From commercial glycyrrhizinum ammoniacale: Tschirch, Cederberg, *Arch. Pharm.* 245, 97 (1907); Voss *et al.*, *Ber.* 70, 122 (1937). Revised method of isoln: Conn, Conn, *J. Lab. Clin. Med.* 47, 20 (1956). Structure: Lythgoe, Trippett, *J. Chem. Soc.* 1950, 1983. Alternate view: Marsh, Levvy, *Biochem. J.* 63, 9 (1956). *Review:* Nieman, *Chem. Weekbl.* 48, 213 (1952). Synthesis of derivatives: Brieskorn, Sax, *Arch. Pharm.* 303, 905 (1970).

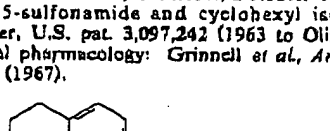


Crystals from glacial acetic acid. Intensely sweet taste. $[\alpha]_D^{25}$ +46.2° (c = 1.5 in alc). Freely sol in hot water, alcohol; practically insol in ether.

Ammonium glycyrrhizinate pentahydrate, $C_{42}H_{65}NO_{16}.5H_2O$, needles from 75% aqueous ethanol, decomp 212-217°. $[\alpha]_D^{20}$ +46.9° (c = 1.5 in 40% ethanol). uv max: 248 nm (ε 11,400). Sol in ammonia water, glacial acetic acid.

Dipotassium salt, $C_{42}H_{60}K_2O_{16}$. *Rizinsan K2 A2*

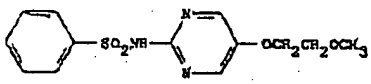
4370. Glyhexamide. *N-[(Cyclohexylamino)carbonyl]-2,3-dihydro-1H-indene-5-sulfonamide; 1-cyclohexyl-3-(5-indanylsulfonyl)urea;* 1-cyclohexyl-3-(5-hydrindenylsulfonyl)urea; SQ 15860; Subose. $C_{16}H_{22}N_2O_3S$; mol wt 322.45. C 59.60%, H 6.88%, N 8.69%, O 14.89%, S 9.95%. Prepd from hydrindene-5-sulfonamide and cyclohexyl isocyanate: Hoechn, Braeuer, U.S. pat. 3,097,242 (1963 to Olin Mathieson). Clinical pharmacology: Grinnell *et al.*, *Am. J. Med. Sci.* 253, 312 (1967).



Crystals from 70% acetone, mp 153-155°.

THERAP CAT: Antidiabetic.

4371. Glymidine. *N-[5-(2-Methoxyethoxy)-2-pyrimidinyl]benzenesulfonamide;* 2-benzenesulfonamido-5-(β-methoxyethoxy)pyrimidine; glycodiazine. $C_{13}H_{15}N_3O_4S$; mol wt 309.35. C 50.47%, H 4.89%, N 13.58%, O 20.69%, S 10.37%. Prepn: Belg. pat. 609,270 corresp to H. Priewe *et al.* U.S. pat. 3,275,635 (1962, 1966 to Schering, AG); Gutsche *et al.*, *Arzneimittel-Forsch.* 14, 373 (1964). Series of articles on pharmacology: *Ibid.* 377-412. Activity: Losert *et al.*, *Ibid.* 23, 1251 (1973). Metabolism: Soyfer *et al.*, *Chim. Ther.* 5, 441 (1970).

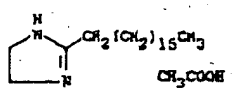


Crystals, mp 152-154°. Soly in ethanol: 0.91%; in toluene: 0.67%.

Sodium salt, $C_{13}H_{14}N_3NaO_4S$. *SH 717, Glycanormal, Gondafon, Lycanol, Redul.* Crystals, mp 221-226°. Sparingly sol in alc. Soly in water at 37°: 70.5%. LD_{50} in mice, rats (g/kg): 1.48, 2.00 i.v.; 5.30, 2.85 orally, Kramer *et al.*, *Arzneimittel-Forsch.* 14, 377 (1964).

THERAP CAT: Antidiabetic.

4372. Glyodin. *2-Heptadecyl-4,5-dihydro-1H-imidazole monoacetate;* 2-heptadecylglyoxalidine acetate; Crag Fruit Fungicide 341. $C_{22}H_{44}N_2O_2$; mol wt 368.59. C 71.68%, H 12.03%, N 7.60%, O 8.68%. Prepn from stearic acid and ethylenediamine: Kiff, U.S. pat. 2,540,171 (1951 to Union Carbide and Carbon).



Light orange crystals, mp 62-68°. d^{20} 1.035. Insol in water, acetone, toluene; sol in isopropanol. The base is a soft greasy wax, mp 94°.

USE: Fungicide.

4373. Glyoxal. *Ethanedial;* biformyl; diformyl; oxalaldehyde. $C_2H_2O_2$; mol wt 58.04. C 41.39%, H 3.48%, O 55.14%. OHCCHO. Prepd by the oxidation of acetaldehyde by nitric or selenious acid: Lubawin, *Ber.* 8, 768 (1875); Wyss, *Ber.* 10, 1366 (1877); Kölln, *Ann.* 416, 230 (1918); Riley *et al.*, *J. Chem. Soc.* 1932, 1881; Ronzio, Waugh, *Org. Syn.* coll. vol. III, 438 (1955); by hydrolysis of dichlorodioxane: Butler, Cretcher, *J. Am. Chem. Soc.* 54, 2988 (1932). Review of commercial development: J. F. Bohmfalk *et al.*, *Ind. Eng. Chem.* 43, 786 (1951). *Review:* A. B. Boese *et al.*, in *Glycols*, G. O. Curme, F. Johnston, Eds. (Reinhold, New York, 1952) pp 125-128.

Yellow prisms or irregular pieces turning white on cooling. d^{20} 1.14. Opaque at 10°, mp 15°, bp_{775} 51°. The vapors are green and burn with a purple flame. *Caution:* Mixtures with air may explode! $n_D^{20.5}$ 1.3826. Sol in anhydr solvents. pH of a 40% aq soln: 2.1-2.7; d_4^{20} 1.27. Polymerizes quickly on standing, on contact with water (violent reaction), or when dissolved in solvents contg water. The anhydr polymer changes to the monomer on heating. Solns of the monomer are obtained on heating the polymer with anethole, phenetole, safrole, methyl nonyl ketone, or benzaldehyde. LD_{50} orally in rats, guinea pigs: 2020, 760 mg/kg, H. F. Smyth *et al.*, *J. Ind. Hyg. Toxicol.* 23, 259 (1941).

Dihydrate, $(OHCCHO)_2.2H_2O$, cryst powder, nonhygroscopic. More sol in hot water than in cold water. Commercially available in anhydr form as cryst dihydrate, or as a 40% aq soln which may contain polymerization inhibitors.

Caution: Moderately irritating to skin, mucous membranes.

USE: In textiles, organic synthesis, glues, biocides.

4374. Glyoxal-Sodium Bisulfite. *1,2-Dihydroxy-1,2-ethanedisulfonic acid disodium salt; glyoxal compound with sodium bisulfite.* $C_2H_4Na_2O_8S_2$; mol wt 266.16. C 9.02%, H 1.51%, Na 17.28%, O 48.09%, S 24.09%. Prepn: Ronzio, Waugh, *Org. Syn.* coll. vol. III, 438 (1955).